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Science Policy Note SPN2016-02

Dermal Absorption: Position Papers from the North American Free Trade Agreement (NAFTA) Technical Working Group (TWG)

(publié aussi en français)

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Executive Summary

This Science Policy Note (SPN) includes information on two dermal absorption position papers that were developed by the North American Free Trade Agreement's (NAFTA's) Dermal Absorption Group, which was an expert working group formed under the NAFTA Technical Working Group (TWG) on Pesticides. While these position papers are discussed in the NAFTA TWG Accomplishments Report (2008-2013)[1] and Health Canada's Pest Management Regulatory Agency (PMRA) has and continues to share these papers with interested stakeholders, the Science Policy Note now provides an opportunity for PMRA to publish these positions for broader dissemination. In addition, the other regulatory bodies involved with this initiative will now also have a source to provide to their stakeholders.

These position papers continue to be reflective of PMRA's current position with respect to the acceptability of in vitro dermal absorption studies as well as modifications to the in vivo test guidelines. They also reflect Health Canada's ongoing commitment to reducing the need for animal testing wherever possible while retaining utility for risk assessment. PMRA continues to be involved in ongoing initiatives designed to reduce, refine and replace the need for animal testing with other NAFTA Regulatory authorities, such as the United Stated Environmental Protection Agency (USEPA), and key stakeholders. The Agency will assess whether the outcome of these efforts requires changes to this Science Policy Note. If so, these changes will be made, accordingly.

The Science Policy Note itself is divides the two position papers into two sections as follows:

Section 1(Position Paper 1): Use of in vitro Dermal Absorption Data in Risk Assessment

Finalized in 2008, this section of the Science Policy Note outlines how the PMRA currently uses in vitro dermal absorption data in a 'Triple Pack'[2] approach. Before this aligned approach was developed, the NAFTA regulatory authorities did not have a formal policy or position on the use of in vitro dermal absorption studies in pesticide risk assessment. Since the development of the position paper, Health Canada's PMRA and other NAFTA agencies, such as the USEPA, have been applying the triple pack approach to the submitted dermal absorption studies.

Section 2 (Position Paper 2): Streamlined OPPTS 870.7600 (Dermal Penetration)

In 2011, a streamlined in vivo dermal absorption test guideline was developed. The goal of this guideline was to detail how to reduce animal use and cost, while maintaining scientific integrity and utility for risk assessment purposes. It also provides additional information on the NAFTA position regarding appropriate doses, durations of exposure, impact of formulations, and tape stripping, which is not found in other North American test guidelines.

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1 North American Free Trade Agreement Technical Working Group on Pesticides - Accomplishments Report for the period of 2008-2013 (http://www.hc-sc.gc.ca/cps-spc/alt_formats/pdf/pubs/pest/corp-plan/nafta-alena-2008-2013/nafta-alena-2008-2013-eng.pdf)

2 'Triple Pack' is the term used to describe a set of rat *in vivo*, rat *in vitro*, and human *in vitro* dermal absorption studies.

Any questions regarding this policy note should be directed to the PMRA's Pest Management Information Service.

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Section 1: NAFTA Dermal Absorption Group Position Paper 1 on Use of in vitro Dermal Absorption Data in Risk Assessment

In 2008, the NAFTA Dermal Absorption Group concluded that in vitro animal and/or human data alone are insufficient for determining the dermal absorption pattern of a given pesticide. This position is based primarily on the lack of a detailed, standardized methodology for in vitro dermal absorption studies. While there have been ongoing efforts to further standardize methodology for these studies, differences (for example, in methodology and experience between and within laboratories) lead to varying results among laboratories. Therefore, use of in vitro data as the sole basis for derivation of a Dermal Absorption Factor (DAF) for human health risk assessment is not recommended at this time.

However, in vitro data may be useful when combined with other information in a weight-of-evidence approach for predicting a DAF. When in vitro data are being submitted to the Agencies, the NAFTA Dermal Absorption Group recommends submission of a data set consisting of a "Triple Pack" of in vitro human and animal studies and an in vivo animal study as most likely to yield verifiable in vitro data that may be used to establish DAFs for risk assessment. Under this approach, if an in vitro technique performed using animal skin is shown to be a good predictor of animal in vivo dermal absorption for a particular compound, then the same technique conducted in vitro with human skin may be useful in extrapolating to humans. In other words, when laboratory studies demonstrate that the ratio of the animal in vitro to in vivo DAF is close to 1, a human in vitro study conducted under the same conditions as the animal test is likely to be a good predictor of human dermal absorption.

$$\text{IF} \quad \frac{\text{Animal in vitro}}{\text{Animal in vivo}} \approx 1 \quad \text{THEN} \quad \text{Human in vitro} \approx \text{Human DAF}$$

The usefulness of the data would necessarily be dependent on the validity and applicability of the experimental design and the quality and integrity of the data.

Under this approach, the following minimal standards should be considered when developing protocols for dermal absorption studies.

1. **Basic study design**. A comparative in vivo/in vitro dermal absorption submission should consist of at least three studies conducted using the same dose/duration regimen: 1) an in vitro study using human skin, 2) an in vitro study using animal (typically rat) skin, and 3) an in vivo animal dermal absorption study. While it is preferred that the studies be conducted concurrently, independently conducted studies may be considered if the experimental conditions are sufficiently similar. An assessment of the experimental conditions and their potential impact on the study results should always be part of the consideration of data applicability.

2. **In vitro guidelines**. In vitro studies should be conducted in accordance with the OECD Guidance Document for the Conduct of Skin Absorption Studies (OECD Series Number 28) (2004).

3. **In vivo guidelines**. In vivo studies should be conducted in accordance with modified U.S. EPA OPPTS Human Effects Test Guidelines for Dermal Penetration (OPPTS 870.7600) (1998).

4. **In vitro reproducibility**. Independent repeat comparative in vitro studies conducted with animal or human skin should be used to demonstrate reproducibility of results.

5. **Replicates or sample size**. Use of an increased number of replicates (i.e., 6 or more replicates per dose/duration) should also increase confidence in the validity and reliability of in vitro study results provided an acceptably low coefficient of variation is maintained.

6. **Regional variability in human skin**. Given that there is considerable regional variability in permeability of human skin, it is important to consider the region of the skin used in comparative rat/human in vitro studies when using in vitro data for derivation of a DAF. For example, there is evidence that skin from the human hand, head and neck regions exhibit higher permeability than trunk skin, which is typically used for human in vitro dermal absorption studies. Therefore, use of skin from less permeable regions for in vitro studies could underestimate dermal absorption, especially in cases where more permeable regions (i.e., hands, head and neck) also correspond to areas of maximum exposure. It is critical, therefore, to consider the location of the human skin used in an in vitro study in characterizing the results of the study.

The NAFTA Dermal Absorption Group strongly encourages that when in vitro data are submitted, these should be submitted as part of a triple pack. This type of data may be useful for providing a baseline for assessing in vitro studies relative to in vivo studies across chemicals, improving the quality of in vitro studies, and laying the groundwork for future use of in vitro studies for derivation of Dermal Absorption Factors for human health risk assessment. Submission of comparative in vivo/ in vitro dermal absorption studies is critical to generating the data needed to validate in vitro methodologies and results.

Section 2: NAFTA Dermal Absorption Group Position Paper 2: Streamlined OPPTS 870.7600 (Dermal Penetration)

The standard OPPTS 870.7600 Dermal Penetration Test Guideline specifies that multiple concentrations of the test material (3-4) and multiple durations of exposure (6 time points) be examined in order for estimates of dermal absorption to cover a variety of use patterns. The Guideline also describes an abbreviated study, in which only 3 time points are used. In practice, however, for both the standard and abbreviated 870.7600, only some of these dose levels and time points are actually used to estimate dermal absorption factors (DAFs).

Over the course of review of dermal absorption studies, the NAFTA Dermal Absorption Group observed that it may be possible to streamline 870.7600 studies and reduce the cost and the number of animals used by testing only the dose levels and time points often used for risk assessment. The dose levels most often used for risk assessment are those that are relevant to occupational and residential exposures, and the time points most often used are those that are protective of all durations in occupational and residential scenarios. Therefore, it is possible, in most cases, to make general recommendations regarding which dose levels and time points are most useful for estimating a DAF.

Importantly, the 870.7600 Test Guideline allows for the use of a reduced number of dose levels and durations of exposure provided these are relevant for the use pattern/s under consideration for risk assessment.

> (c) **Test Procedure**—(1) **Variation of procedure.** The basic study described is designed to cover the entire range of doses and durations of exposure expected for a pesticide designed for a wide variety of uses. It is frequently possible to cover the use pattern at risk for a particular pesticide with a lesser number of doses and durations of exposure. In the case of pesticides having a limited pattern of use, Registrants may, after consultation with the Agency, perform only those doses and durations of exposure that are applicable to the use pattern which is being considered for risk assessment.

In 2011, the NAFTA Dermal Absorption Group provided general recommendations herein that would allow streamlining of the OPPTS 870.7600 studies to limit dose levels and durations of exposure to those that are relevant for the product use pattern when justified by sound, scientific rationale for future submissions to the NAFTA Regulatory authorities. This will have the benefits of reducing animal use while retaining utility for risk assessment (see **Table 1**).

Table 1 Comparison of streamlined, basic and abbreviated OPPTS 870.7600 protocol (Dermal Penetration)

	Streamlined[a]	Basic[b]	Abbreviated[b]
N (Animals per data point)	At least 6	4	4
Concentration	Only those resulting in doses expected for occupational and residential scenarios Inclusive of lowest practical exposure Justification of all dose levels required	3-4, log intervals, span doses used in field (for example, 1.0, 0.1, 0.01 and 0.001 mg/cm^2)	Same as basic
Exposure duration	10 h and 24 h A satellite group may be added for determining bioavailability of skin-bound residue (justify duration)	0.5, 1, 2, 4, 10, and 24 h *A satellite group out to 14-21 days may be added to determine bioavailability of skin-bound residue	1, 10, and 24 h *A satellite group out to 14-21 days may be added to determine bioavailability of skin-bound residue
Total Animals Used in study	At least 12 per dose At least 18 per dose (with satellite)	72-96 (no satellite) 84-112 (with satellite)	36-48 (no satellite) 48-64 (with satellite)

[a] Protocol proposed in this position paper
[b] As described in OPPTS 870.7600 Test Guidance

OPPTS 870.7600 Recommendations

The following are also recommendations for variations of procedure that the NAFTA Dermal Absorption Group considered as being appropriate, when adequate justification is provided. However, Agencies are willing to review protocols and provide additional guidance, if needed.

1) Concentration

The 870.7600 Test Guideline recommends testing of 3-4 different concentrations of the test chemical at log intervals that span the concentrations used in the field. This Position Paper recommends that the concentrations tested be limited to those that will result in doses (in mass/area) that are relevant to anticipated occupational and residential exposures. Doses should be justified and inclusive of the lowest practical exposure.

2) Formulation

The chemical constituents of the pesticide formulation can greatly impact dermal absorption. For this reason, it is recommended that dermal absorption studies be performed using the formulation blank. If multiple formulations are available for a particular pesticide and bridging to other

formulations with a representative formulation is desired, justification for the use of the representative formulation should be provided. This justification should address whether or not dermal absorption is likely to be reduced or enhanced for the representative formulation relative to other formulations.

3) Number of animals

The OPPTS 870.7600 Test Guideline recommends the use of 4 animals per dose per time point. The NAFTA Dermal Absorption Group recommends increasing this number to 6 or more animals per dose per time point. Fewer sampling times and fewer doses will be available to assess the dermal absorption profile of the chemical in a streamlined protocol, which could be further complicated by experimental variability. Increasing the number of animals above 4 per data point may decrease variability.

4) Durations of exposure

The OPPTS 870.7600 Test Guideline recommends exposure durations of 0.5, 1, 2, 4, 10, and 24 h for the basic study and 1, 10, and 24 h for the abbreviated study. This Position Paper recommends that exposure durations can be further streamlined to a 10 h exposure (for occupational scenarios) and a 24 hour exposure (for residential scenarios). Skin should be washed after exposure. Tape stripping after/in place of washing is not recommended, due to laboratory variability in kinds of tape and technique. A satellite group or groups, that is/are monitored for a duration of time after the 10 h exposure and wash, may also be included to address the bioavailability of skin-bound residues. The duration of time selected for any satellite groups should be justified.

5) Skin-bound residues

Skin-bound residues are the fraction of the adsorbed dose that is not removed by washing. These residues are assumed to be bioavailable and are included with the absorbed dose in calculating a DAF by all NAFTA regulatory agencies. However, it may be possible to reduce skin-bound residues to only those that are bioavailable, thus reducing the DAF. Experimentally, this could be achieved by including a satellite group or groups that is/are monitored for a duration of time after the 10 h exposure and wash. The study duration for any satellite groups should be justified. Justifications could be based on biology (e.g. complete turnover of cornified epithelium in rats by 21 days) or data (e.g. demonstration of no increases of absorption over time). Use of tape stripping in place of washing or to rule out skin-bound residues is not recommended, due to laboratory variability in kinds of tape and technique.

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